REMARKS/ARGUMENTS

I. Status of the Claims

After entry of this amendment, claims 121-145 are pending, claims 1-120 having been previously canceled.

Applicants note that the Examiner did not address the amendment to claim 143, wherein the duplicated "E2 and E4" was deleted, which was made in the amendment filed April 29, 2005 and May 19, 2005. Unless the Examiner notifies Applicants otherwise, it will be assumed that the amendment to claim 143 was entered.

II. Drawings

The Examiner has objected to the drawings because the packaging signal that should be in the last vector in Figure 17A is allegedly missing. Applicants refer the Examiner to the amended Figures 17A and 17B submitted with the Request for Continued Examination filed April 29, 2005. As amended therein, Figures 17A and 17B indicate the presence of packaging signals at the right end of the last vectors in both figures. Support for the correction to Figure 17A is provided in the drawing as originally filed, wherein recombination between the first two vectors at the second "X" would generate the last vector with a packaging signal between the AAV.ITR and Ad.ITR at the right end of the vector. Support for the correction to Figure 17B to is provided in the drawing as originally filed, wherein recombination between the first two vectors at "X" would generate the last vector with a packaging signal between the AAV.ITR and Ad.ITR on the right end of the vector. Applicants note, however, that the marked-up copy of the figures filed April 29, 2005 has two errors: (1) the correction to add the packaging signal to the last vector in Figure 17A shows the packaging signal above rather than below the vector; and (2) the correction to add the packaging signal to the last vector of Figure 17B is inadvertently missing. Accordingly, Applicants attach a corrected marked-up copy drawing sheet 20 with Figures 17A and 17B in the Appendix following the Remarks.

III. Specification

The Examiner has objected to the specification because it allegedly introduces new matter. The Examiner alleges that no support is found in the original disclosure for the amended page 10, wherein the IRs are stated to be 1.2kb and the "lower" vector comprises the "same" IRs. Applicants respectfully disagree. Support for the amended page 10 is provided in the specification as originally filed at page 10, lines 14-21. Support for the IRs being 1.2kb is provided by "the first generation Ad.AAV vector (~34kb) contains two 1.2kb inverted homology elements flanking the transgene cassette." Support for the "lower" vector comprising the "same" IRs is provided by "recombination between two inverted repeats (IR) present in one Ad.AAV vector." Because the first and second Ad.AAV vectors in Figure 17A are the same vector, the IRs on these vectors must also be the same.

The Examiner also alleges that no support is found in the original disclosure for the amended page 86, wherein it is stated that pCD1 is depicted in Figure 9. Applicants respectfully disagree. In Figure 9, the second vector is denoted as pAD5 shuttle plasmid (pBHG10, pcD1). Thus, pCD1 is clearly depicted in Figure 9.

The Examiner has objected to the disclosure because the last sentence prior to the description of 17B on amended page 86 appears to be a sentence fragment. Applicants have deleted this sentence fragment, thereby rendering moot this ground of objection to the disclosure.

IV. Claim Rejections

The Examiner has maintained the rejection of claims 121-145 as not being enabled. The Examiner alleges that the skilled artisan would have had to conduct undue unpredictable experimentation in order to practice the claimed invention. In particular, the Examiner alleges that development of adenoviral vectors for gene therapy is a complex art that requires great skill, and that simultaneous modification of integrative ability and tropism of the vector requires a complex series of manipulations of the adenoviral genome that are highly unpredictable given the lack of guidance in the specification. Specifically, the Examiner alleges

that the specification does not teach how the anti-parallel strand can be modified to express a modified fiber protein, when the fiber protein is normally expressed from the parallel strand. Applicants respectfully disagree for the following reasons.

As an initial matter, Applicants confirm that the Examiner is correct in surmising that the "parallel" and "anti-parallel" strands of adenovirus DNA as used in this application correspond to the "r" and "l" strands as used in the art. The Examiner is also correct that the art teaches that the fiber protein is encoded by the "parallel" or "r" strand of the adenovirus genome. Finally, the Examiner notes that in Figure 18 it appears that the "parallel" strand encodes the chimeric fiber protein. Again, the Examiner is correct, but Applicants fail to see how this example supports the allegation that the terminology used in the specification is confusing.

The specification at page 19, lines 27-30, provides that "the fiber protein is encoded on the anti-parallel strand of DNA. To simplify the vector diagrams, the fiber sequences are shown on the parallel strand even though the gene is located on the anti-parallel strand." Based on this, one skilled in the art would immediately recognize that the fiber gene in this application is encoded on the anti-parallel strand, regardless of what is shown in the figures or otherwise known in the art. Thus, even though the fiber gene is encoded by the parallel strand in the adenovirus genome, it is encoded by the anti-parallel strand on the adenoviral vectors of the instant invention. Even though it appears in Figure 18 that the fiber sequences are encoded on the parallel strand, they are encoded on the anti-parallel strand. Applicants respectfully submit that the skilled artisan would not be confused by the terminology in the specification, and that the specification clearly provides that the fiber gene in the claimed adenoviral vectors is encoded on the anti-parallel strand.

Whether undue experimentation is required is based on a conclusion reached by weighing the *Wand*s factors, which include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of unpredictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of

the disclosure. Applicants respectfully submit that armed with the specification, one skilled in the fields of molecular, cell and viral biology, which the Examiner regards as the disciplines utilized in the instant invention, would be able to make and use adenoviral vectors having the fiber gene encoded by the anti-parallel strand without undue experimentation.

Here, the Examiner argues that undue experimentation would be required to make and use the adenoviral vectors of the invention given: (a) the high level of unpredictability in the art; and (b) the fact that Applicants have not exemplified the construction of an adenoviral vector with the fiber protein encoded on the anti-parallel strand.

Regarding the alleged high level of unpredictability in the art of development of adenoviral vectors for gene therapy, Applicants respectfully disagree with the Examiner's assessment. Here, the issue is whether there is a high level of unpredictability in constructing adenoviral vectors that can deliver and express foreign genes in infected target cells or tissues. Adenoviral vectors that are suitable for expressing foreign genes in infected cells or tissues are well-known in the art. Armed with the specification, one of ordinary skill in the disciplines of molecular, cell and viral biology would be able modify such adenoviral vectors so that they can infect different cells or tissues, integrate into the genome of the infected cells, and express foreign genes. The specification provides guidance for altering or modifying fiber proteins, which mediate tropism for desired target cells. The specification provides guidance for generating modified adenoviral vectors that have AAV ITR sequences, which mediate recombination in infected cells. The specification provides guidance for generating modified adenoviral vectors that can express foreign genes under the control of heterologous promoters. None of the above is contested by the Examiner. In addition, the level of one of ordinary skill interested in developing adenoviral vectors is very high, given that adenoviral vectors have been used in the art for more than a decade. Thus, Applicants respectfully submit that, given the ample guidance in the specification and the high level of skill of one of ordinary skill, the development of adenoviral vectors with altered or modified tropism which can infect target cells or tissues, integrate into the genome, and express foreign genes, is not a highly unpredictable art.

Based on the foregoing, the critical issue appears to be that the specification allegedly does not teach how to express an altered or modified fiber gene from the anti-parallel strand. Applicants respectfully submit that armed with the specification, the skilled artisan would be able to make and use an adenoviral vector with the altered or modified fiber gene on the anti-parallel strand without undue experimentation.

To generate an adenoviral vector having an altered or modified fiber gene encoded on the anti-parallel strand is merely a matter of using standard recombinant DNA techniques, bearing in mind the structure and organization of the adenoviral vector that is to be modified. There are many ways to generate such an adenoviral vector, for example, by "flipping" the entire adenovirus E2-E4 region so that the E2 and E4 genes are encoded on the parallel strand and the fiber gene is encoded on the anti-parallel strand, or by replacing the fiber gene with a transgene capable of expressing an altered or modified fiber gene in the anti-parallel orientation. In this case, one can generate a construct having the coding region of the altered or modified fiber gene under control of a regulatory element (*i.e.*, a transgene). The specification at page 16, lines 6-10, provides that vectors of the instant invention may be operatively linked to a transgene sequence encoding a polypeptide, such as a viral fiber protein. The specification at page 16, line 26 to page 17, line 2, also provides that vectors of the instant invention may be linked to a regulatory element that may direct the expression of the transgene. The regulatory element may regulate the amount, timing, or cell-type of expression of the transgene. Thus, the specification clearly contemplates and describes constructing adenoviral vectors with the fiber gene under control of a regulatory element. One skilled in molecular biology, armed with the specification, would be able to generate a transgene construct with a viral fiber protein gene under control of a regulatory element. Mere routine techniques would be required to generate a transgene construct that can be expressed in a particular target tissue.

Second, the fiber gene transgene can be introduced into the adenoviral vector at a site on the anti-parallel strand that does not interfere with the expression and function of the adenovirus replication proteins, in particular E2 and E4. One skilled in the art of viral biology would be able to identify sites in the claimed adenoviral vectors given the biology of adenovirus

and the physical constraints of the adenoviral vectors of the invention. Here, the specification provides examples of the modified or altered fiber genes being inserted between the E2 and E4 genes, although one of skill could readily identify other possible locations. All that is needed is to insert the fiber gene transgene in the anti-parallel orientation instead of the parallel orientation. Again, mere routine techniques would be required to generate an adenoviral vector that can express the modified or altered fiber gene in infected cells.

The Examiner alleges that expression of the modified fiber proteins must be regulated in the same way as endogenous fiber proteins during adenovirus infection. Applicants respectfully disagree. Although the percentage of infectious virus produced is lower, it is known in the art that temporally regulated expression of the fiber protein from the vector itself is not required for proper packaging of adenoviral vectors in infected cells (see Legrand et al., 1999, *J. Virol.* 73:907-919). As shown in Legrand, expression of the fiber gene can be driven by the CMV promoter, and the fiber protein can be provided in *trans* to generate infectious virus. Based on this, one skilled in the art could reasonably expect to generate infectious virus by infecting cells with an adenoviral vector expressing a modified or altered fiber protein driven by a promoter that is not regulated in the same way as endogenous fiber proteins.

Applicants respectfully submit that one of ordinary skill in the art of viral biology would be able to select for modified adenoviral vectors that fulfill the requirements of the claimed invention. The issue for enablement is not whether any experimentation is needed, but whether the experimentation is undue. In *Wands*, the technology involved production of monoclonal antibodies and selection of monoclonal antibodies with a desired activity. The court found that the experimentation needed was routine, so that even though only a small fraction of the monoclonal antibodies generated would have the desired activity, the experimentation was determined not to be undue.

Here, generating modified or altered fiber gene transgenes under control of a promoter, inserting them in the anti-parallel strand of an adenoviral vector, and selecting for modified adenoviral vectors that produce infectious virus upon infection of target cells merely

require routine techniques. Using the specification as a guide, one of ordinary skill would be able generate and identify adenoviral vectors that satisfy the requirements of the claimed invention using standard protocols in molecular, cellular and viral biology. Thus, Applicants respectfully submit that, as in *Wands*, although a great deal of experimentation may be required, and the likelihood of any individual construct being successful may be small, merely routine techniques are required and, as such, the experimentation needed is not undue.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

Neil G. Miyamoto
Reg. No. 50,370

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-326-2400
Fax: 415-576-0300
Attachments
NGM:ym
60621472 v1